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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/978,297	10/17/2001	Oron Yacoby-Zeevi	01/22716	5033

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EXAMINER	
HUTSON, RICHARD G	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/978,297	YACOBY-ZEEVI, ORON	
	Examiner	Art Unit	
	Richard G. Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-9,11-17,19-37 and 51-84* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 7-9, 11-17, 19-37 and 51-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants amendment of the specification and claims 1, 7, 13, 21, 26, 31 and the addition of new claims 51-84, in the paper of 1/12/2006, is acknowledged. Claims 1-5, 7-9, 11-17, 19-37 and 51-84 are present for examination. Applicants' arguments filed on 1/12/2006, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 51-84 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of improving embryo implantation, the method comprising contacting an embryo with an effective amount of purified recombinant heparanase having at the amino acid sequence of SEQ ID NO: 1 and inserting the embryo in a receptive uterus, wherein said embryo and uterus are from the same species, does not reasonably provide enablement for any method of improving embryo implantation, the method comprising contacting any embryo with an effective amount of purified recombinant heparanase having a mere 90% homology to SEQ ID NO: 1 and inserting the embryo in any receptive uterus. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 51-84 are so broad as to encompass any method of improving embryo implantation, the method comprising contacting any embryo with an effective amount of purified recombinant heparanase having at mere 90% homology to SEQ ID NO: 1 and inserting the embryo in any receptive uterus, wherein said embryo and uterus are from the same species. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of heparanse variants broadly encompassed by the claims, including methods involving any the use of any heparanase variant having a mere 90% homology to SEQ ID NO: 1.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is

unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass any method of improving embryo implantation, the method comprising contacting an embryo with an effective amount of purified recombinant heparanase having a mere 90% homology to SEQ ID NO: 1 and inserting the embryo in any receptive uterus, because the specification does not establish: (A) regions of the protein structure which may be modified without effecting heparanase activity; (B) the general tolerance of heparanases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of a heparanase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the heparanase activity necessary to practice the claimed methods and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those methods of the claimed genus.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including methods of use of those heparanases having a mere 90% homology to SEQ ID NO: 1. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those methods having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those species in which the disclosed methods are successful is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicants comments and the board decision in the paper submitted on 1/12/2006, are acknowledged, however, are not found persuasive in the withdrawal of the above rejection. Applicants are reminded that the factors necessary for the determination of the enablement of the instant claims and that of the referred to board decision are different. Consideration of those factors as discussed above have resulted in the current rejection for the reasons stated above.

Claims 1-5, 7-9, 11, 12, 13-17, 19, 20, 21-25, 26-30, 31-37 and 51-84 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-5, 7-9, 11, 12, 13-17, 19, 20, 21-25, 26-30, 31-37 and 51-84 are rejected under this statue because the recitation in claims 1, 7, 13, 21, 26, 31, 51, 56, 61, 68, 73 and 78 that states " wherein said purified recombinant heparanase can elicit anti-heparanase antibodies" is not supported by the specification at the time of filing and is thus considered new matter. Applicants amendment of the specification in the paper of 1/12/2006 to incorporate related subject matter from the fourth prior CIP of the instant application, now U.S. Patent No. 5,968,822, is acknowledged, however, this is not considered to support applicants amendment as stated above to the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 7-9, 11, 12, 13-17, 19, 20, 21-25, 26-30, 31-37 and 51-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fuks et al., Gough et al., (U.S. Patent No: 5,962,321) and Goshen et al. (Molecular Human Reproduction, Vol 2, No. 9, pp 679-684, 1996, see IDS).

The rejection is stated in the previous office action as it applies to previous claims 1-5, 7-9, 11, 12, 13-17, 19, 20, 21-25, 26-30 and 31-37. In response to this rejection applicants have amended claims 1, 7, 13, 21, 26, 31 and the added new claims 51-84 and traverse the rejection as it applies to the newly amended claims. Claims 51-84 are included in this rejection for the same reasons originally stated for claims 1-5, 7-9, 11, 12, 13-17, 19, 20, 21-25, 26-30 and 31-37. Claims 51-84 are drawn to the same methods as claims 1-5, 7-9, 11, 12, 13-17, 19, 20, 21-25, 26-30 and 31-37, with the exception that the are not drawn to a method of use the recombinant heparanase of SEQ ID NO: 1, but rather a method of use the recombinant heparanase having at least 90% homology to SEQ ID NO: 1. Thus as the original rejection stated that Fuks et al. teach the purification of heparanase obtained from human SK-HEP-1 cells, and it is recognized that the heparanase taught by Fuks et al. inherently has the amino acid sequence of SEQ ID NO: 1., these claims are included in the rejection as being obvious for the same reasons previously stated for claims 1-5, 7-9, 11, 12, 13-17, 19, 20, 21-25, 26-30 and 31-37.

Applicants submit that the combination of all references is not obvious and is at best an invitation to try, however, to promote the prosecution of the subject application applicants have amended the claims to require that the claimed heparanase be pure

enough to elicit anti-heparanase antibodies and further submit a declaration discussing this and thus submit that the rejection be withdrawn.

Applicant's complete argument is acknowledged and has been carefully considered, however, continues to be found non-persuasive on the following basis.

As a preliminary note for applicants, applicants statement that they have required that the claimed heparanase be pure enough to elicit anti-heparanase antibodies, is not accurate, as applicants claims are to a method of use of a purified recombinant heparanase, wherein said purified recombinant heparanase "can elicit anti-heparanase antibodies". Applicants amendment does not require that the claimed heparanase be pure enough to elicit anti-heparanase antibodies , but merely that the heparanase of the claimed method "can elicit anti-heparanase antibodies".

As previously stated, the preparation taught by Fuks et al. is that of an isolated heparanase, from the same source as applicants claimed heparanase and thus Fuks et al. continues to make obvious applicants claimed isolated heparanase protein for all of the reasons of record. Applicants comments that applicants are not (merely) claiming "an isolated heparanase" but rather a heparanase protein "that can elicit anti-heparanase antibodies" are acknowledged and it is the position of the office that the "heparanase" protein taught by Fuks et al. "can elicit anti-heparanase antibodies" even if the heparanase protein taught by Fuks et al. was in a composition that "did not elicit anti-heparanase antibodies". The limitation/characteristic that the heparanase of the claimed invention "can elicit anti-heparanase antibodies" is an inherent limitation/characteristic of the isolated heparanase taught by Fuks et al.

Thus claims 1-5, 7-9, 11, 12, 13-17, 19, 20, 21-25, 26-30, 31-37 and 51-84 remain obvious over Fuks et al., Gough et al. and Goshen et al.

Conclusion

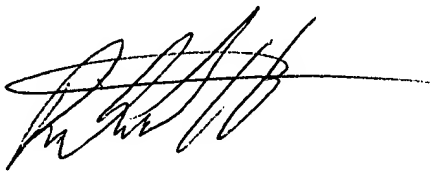
Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is (571) 272-0930. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

rgh
3/21/2006